The Office states in the Advisory Action (Paper No. 21) that the After Final Amendment filed December 18, 1996, does not provide "objective evidence," which address the caveats under 35 U.S.C. § 112, first paragraph, set forth in Paper Nos. 16 and 18. Applicants respectfully disagree, but herein address each caveat set forth in each of these papers in order to be fully responsive to establish that the claimed invention is fully and adequately described in the specification as originally filed.

The Office alleges that definitive support in the specification showing that applicants were in possession of the instantly claimed HIV-1 antigens and that applicants contemplated employing said antigens in the generation and isolation of HIV-1-specific antisera has not been provided. Applicants respectfully disagree. Applicants were clearly in possession of the DNA restriction fragments of plasmid λ-J19 of the claimed invention as set forth at page 4, lines 3-26. In addition, applicants specifically provide for the contemplation and possession of the claim-designated DNA fragments of approximately *Kpn*I (6100) to approximately *Bgl*II (9150); approximately *Kpn*I (3500) to approximately *Bgl*II (6500); and approximately *Pst* (800) to approximately *Kpn*I (3500) as set forth at page 4, line 34 through page 5, line 9. At page 13, lines 13-16, applicants specifically teach that the DNA of the invention can be used for "achieving the expression of LAV viral antigens for diagnostic purposes as well as for the production of a vaccine against LAV." Moreover, it is specifically provided in the specification that "[o]f particular advantage in that respect are the DNA fragments coding for core (gag region)

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
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and envelope proteins, particularly the DNA fragment extending from Kpn I (6 100) to BglII (9 150)." (Specification at 13, lines 16-19).

The methods of making the antigens of the claimed invention are further set forth at page 13 of the specification. Therein, several methods are described:

> a) DNA can be transfected into mammalian cells with appropriate selection markers by a variety of techniques, calcium phosphate precipitation, polyethylene glycol, protoplast-fusion, etc. .
>
> b) DNA fragments corresponding to genes can be cloned into expression vectors for E. coli, yeast or mammalian cells and the resultant proteins purified.
>
> c) The proviral DNA can be "shot-gunned" (fragmented) into procaryotic expression vectors to generate fusion polypeptides. Recombinant producing antigenically competent fusion proteins can be identified by simply screening the recombinants with antibodies against LAV antigens.
>
> d) The invention also relates to oligopeptides deduced from the DNA sequence of LAV antigen-genes to produce immunogens and antigens and which can be synthesized chemically.
>
> All of the above (a-d) can be used in diagnostics as sources of immunogens or antigens free of viral particles, produced using non-permissive systems, and thus of little or no biohazard risk.

(Specification at 13, line 20 through page 14, line 4). Therefore, applicants specifically address how to use the described fragments of the claimed invention to make the claim-designated antigens.

In addition, applicants teach that the invention relates to "vaccine compositions whose active principle is to be constituted by any of the expressed antigens, i.e., whole antigens, fusion polypeptides or oligopeptides." (Specification at 14, lines 9-12). Of course, the production of antibodies derived from these antigens necessarily flows from the use of an antigen in a vaccinating or immunogenic composition, as one having skill in the art would immediately

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, D.C. 20005
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appreciate. Therefore, applicants submit that definitive support for the claimed invention has been provided by the specification as originally filed..

The Office further indicates that the instantly claimed methods of producing to HIV-1 antigens are not enabled. (Paper No. 18 at 3). Applicants submit that this statement is unsupported. According to the Office Action, this rejection is based on a lack of an adequate written description, not lack of enablement. The written description requirement of § 112 is separate and distinct from the enablement requirement. Vas Cath Inc. v. Mahurkar, 19 U.S.P.Q.2d 1111, 1116-17 (Fed. Cir. 1991); and M.P.E.P. Section 2161. Accordingly, applicants submit that this statement is improper. In the event that an enablement rejection is intended, applicants respectfully request clarification of the rejection.

The Office states that "the ability of [the claim-designated] restriction fragments to actually encode the recited HIV-1 antigens is not taught nor is it reasonably suggested by the prior art." (Paper No. 18 at 4). To support this assertion, the Office states that nucleotide sequence data of the claim-designated fragments identifying the initiation and termination codons is not taught. Thus, it is concluded that the specification does not indicate the coding potential of the claim-designated fragments. Applicants submit that this conclusion is incorrect.

In response, applicants submit Rabson and Martin, "Molecular Organization of the AIDS Retrovirus", *Cell* 40:477-80 (March 1985)(Exhibit 1). Rabson and Martin teach the molecular organization of the HTLV-III retrovirus. Therein, one can readily ascertain that restriction fragments recited in the claims are representative of coding regions for the production of

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FARABOW, GARRETT
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1300 I STREET, N.W.
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antigens. For example, claim 23 recites the restriction site KpnI at about coordinate 6100 to the restriction site BglII at about coordinate 9150 of plasmid λ-J19. Locating these approximate coordinates set forth in Figure 1 of Rabson and Martin, one of skill in the art would appreciate that this restriction fragment encodes the env region of HIV-1. Similarly, claim 33 recites the restriction site PstI at about coordinate 800 to the restriction site KpnI at about coordinate 3500 of plasmid λ-J19. As set forth in Figure 1 of Rabson and Martin, this restriction fragment most likely encodes the gag region of HIV-1. Accordingly, applicants submit that Rabson and Martin confirm that these restriction fragments are representative of coding regions for the production of antigens.

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Moreover, applicants provide Wain-Hobson et al., "Nucleotide Sequence of the AIDS Virus, LAV", *Cell* 40:9-17 (1985)(Exhibit 2). Wain-Hobson et al. describe the full length sequence of LAV and particularly of the λ-J19 plasmid. As one can see from this reference, the claim-recited restriction fragments encode coding regions of HIV-1 and therefore, antigens for these regions are clearly ascertainable.

In any event, however, the regions need not even encode full length proteins, i.e., gag, pol, or env, in order to be antigenic. Rather, the restriction fragment may encode regions that, do not comprise the full length gag, pol, or env polypeptide, yet maintain an antigenic use for the production of antibodies, for example. Indeed, one having skill in the art would be more than capable of taking a restriction fragment of the claimed invention, placing it in an expression vector, transforming a host cell with the fragment, and expressing the oligopeptide encoded

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N. W.
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thereby. This simple and known method of producing an oligopeptide is well-established in the art as described in the specification. (Specification at 13, lines 20-27).

The antigenic activity of the peptide can then be readily ascertained as demonstrated in Allan et al., "A New HTLV-III/LAV Encoded Antigen Detected by Antibodies from AIDS Patients", Science, 230:810-813 (1985)(Exhibit 3); Crowl et al., "HTLV-III *env* Gene Products Synthesized in E. Coli Are Recognized by Antibodies Present in the Sera of AIDS Patients", Cell, 41:979-986 (1985)(Exhibit 4); Casey et al., "Human T-Cell Lymphotropic Virus Type III: Immunologic Characterization and Primary Structure Analysis of the Major Internal Protein, p24", *J. of Virol.* 55(2):417-423 (1985)(Exhibit 5); and Parravicini et al., "Immunhistochemical Reactivity of Anti-LAV p18 Monoclonal Antibody in Lymphnodes from PGL and AIDS Patients", *Boll. Ist. Sieroter*, Milan, 64:5-7 (1985)(Exhibit 6). Each of these references demonstrate the purview of the skilled artisan at the time the claimed invention was made to ascertain the immunogenic activity of HIV gene products. Thus, it was readily manifest to one having skill in the art as to how to determine the antigenicity of the claim-recited restriction fragment's expression product.

Applicants submit that under the written description requirement of the first paragraph of § 112, appellants need only show that they were in possession of the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). In determining whether a particular chemical is possessed by an applicant as conveyed in the specification, applicants must

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, D.C. 20005
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define the chemical by more than just its biological or intended function. Fiers v. Revel, 25 U.S.P.Q.2d 1601, 1605 (Fed. Cir. 1993).

The claims at issue in Fiers were directed to a DNA consisting essentially of a DNA coding for a human fibroblast interferon-beta polypeptide. Fier's priority document did not teach the nucleotide sequence of the claimed DNA. Rather, the claim was based upon the functional limitation that the claimed DNA encoded a human fibroblast interferon-beta polypeptide.[1] The Federal Circuit's analysis of this case revolved around whether or not the DNA was adequately described in the specification. In affirming the Board's conclusion that Fier's priority application did not demonstrate conception of the claimed DNA, the court stated that "irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility." (Id. at 1604). Instead, the Federal Circuit held that "[c]onception of a substance *per se* without reference to a process requires conception of its structure, name, formula, or definitive chemical or physical properties." (Id. at 1605). Thus, applicants must define the substance by more than it biological activity or function. (Id.)

In addition, the Federal Circuit in Fiers relied on its previous decision in Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200 (Fed. Cir.), cert. denied sub. nom., 502 U.S. 856, 112 S. Ct. 169, 116 L.Ed.2d 132 (1991), wherein it was stated that:

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[1] The interference count in *Fier* reads: "A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide." *Id.* at 1603.

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
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> Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property . . . because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

(Amgen at 1206). In compliance with the standards set forth in Vas-Cath, Fiers, and Amgen, appellants have described the antigens recited in the claims by both the method for its preparation as well as its chemical and physical properties clearly demonstrating possession of the claimed invention.

The specification clearly defines the restriction fragments by its chemical and physical properties. The claims recite that the restriction fragments are specifically derived from the λ-J19 plasmid, which was deposited in the C.N.C.M. under No. I-338 on September 11, 1984. (Specification at 14, lines 23-27). Unlike Fiers, applicants do not define the restriction fragments by their intended biological function, i.e., to encode the gag, pol, or env regions of HIV-1. Rather, the claims specify the restriction sites and the approximate coordinates for each of the claim-recited fragments. Moreover, applicants define the antigens by its method of preparation as set forth above. Thus, applicants clearly possessed the restriction fragments and the antigens as recited in the claims.

In view of the foregoing, applicants respectfully submit that the rejection is improper. Withdrawal of the rejection is respectfully requested.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N. W.
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Claim 23 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Putney et al. Applicants respectfully traverse the rejection.

Applicants claim benefit of prior application Serial No. 06/771,230 filed on August 30, 1986. As shown above, the prior application, containing the same specification as here, adequately discloses the claimed invention for purposes of 35 U.S.C. § 112, first paragraph.. Putney et al. was published December 12, 1986, after applicants' priority date. Thus, Putney et al. is not prior art to this application. Thus, this rejection is in error and should be withdrawn.

Claims 23, 32, and 33 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Luciw and Dina. Applicants respectfully traverse this rejection.

Applicants claim priority to Great Britain priority document, GB 84 23659 filed September 19, 1984. The priority document antedates even the earliest date for the Luciw and Dina document. Since the prior application and the priority document adequately disclose the invention for purposes of 35 U.S.C. § 112, first paragraph, the Luciw and Dina document is not prior art to this application. This rejection is in error and should be withdrawn.

Applicants believe that this application is now in condition for allowance. In the event the Examiner disagrees, he is invited to call the undersigned to discuss the remaining issues.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested, and the fee should also be charged to our Deposit Account.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
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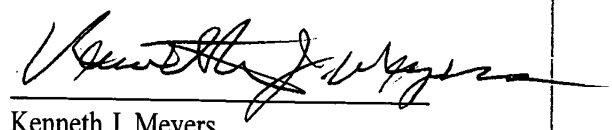
Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: 

Kenneth J. Meyers
Reg. No. 25,146

Dated: March 21, 1997

Exhibits 1-6

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FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, D.C. 20005
202-408-4000